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Ontogeny of fetal plasma proteins

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In the human embryo of 4 weeks' gestation, the yolk sac is a clearly defined vesicle, but the liver is little more than a diverticulum of hepatic buds and ducts. Yet, this rudimentary liver, developing in an embryo which has a crown-rump length of only 4 to 5 mm, is already capable of synthesizing prealbumin, albumin, α-fetoprotein, α_1-antitrypsin, orosomucoid, α_2-macroglobulin, C'1-esterase inhibitor, β_{1C}, β-lipoprotein, hemopexin and transferrin. At 5 weeks' gestation, hepatic lobes can be distinguished and synthesis of ceruloplasmin is detectable. By 5.5 weeks of gestation, hepatic synthesis of fibrinogen can be demonstrated in an occasional embryo[1].

The liver is not the only source of such proteins as albumin and prealbumin. By 4.5 weeks of gestation, the yolk sac synthesizes prealbumin, albumin, α_1-antitrypsin, α-fetoprotein and transferrin (Fig. 1). Indeed, with

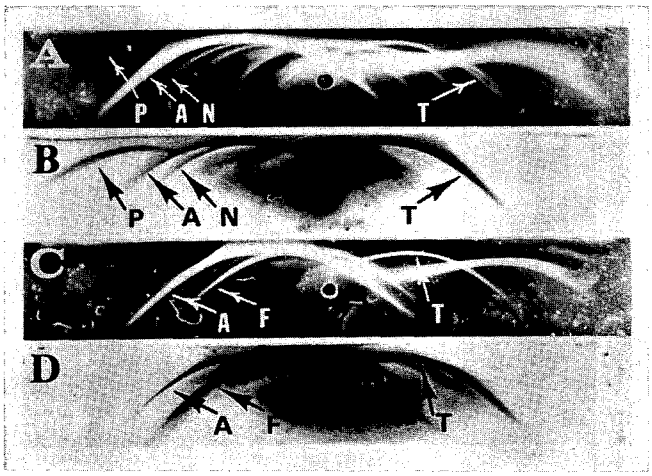

Fig. 1. Immunoelectrophoresis (A) and autoradiograph (B) of yolk sac culture fluid, embryo C9-68 of 5.5 weeks' gestation, with added adult serum and developed with rabbit antiserum against adult serum proteins. Immunoelectrophoresis (C) and autoradiograph (D) of yolk sac culture fluid of embryo C9-68 with added fetal serum and developed with rabbit antiserum against fetal serum proteins. Arrows P, A, N, F and T indicate prealbumin, albumin, α_1-antitrypsin, α-fetoprotein and transferrin, respectively[2].

the exception of albumin, the synthesis of each of these proteins by the yolk sac by 5.5 weeks of gestation is equal to or greater than the synthesis of these proteins by equivalent amounts of liver[2]. However, the yolk sac regresses in development as gestation proceeds, and synthesis of these proteins by the yolk sac decreases noticeably. Although the liver and yolk sac seem to be the major sources of α-fetoprotein, the embryonic gastrointestinal tract is capable of producing small amounts of α-fetoprotein, and in an occasional conceptus, the kidney or the placenta seem capable of synthesizing detectable amounts[3].

All mammals thus far investigated have been shown to have a homologue of α-fetoprotein. Homologues of α-fetoprotein have also been demonstrated in birds[4] and even sharks[5]. The data indicate that the capacity to synthesize α-fetoprotein must have existed in sharks for more than 180 million years and perhaps for as long as 340 million years. If, as also seems likely, shark, avian and mammalian α-fetoproteins did not arise in each class independently, then cistrons for α-fetoprotein appeared before the first appearance of the elasmobranchs, or at least more than 400 million years ago. The major sites of α-fetoprotein synthesis in birds and mammals, as in sharks, are derived from the entoderm of the embryonic foregut including the yolk sac. Since α-fetoprotein synthesis in mammals and sharks takes place in the liver, the absence of α-fetoprotein synthesis in avian liver suggests that this capacity was lost to birds during evolution. In both birds and mammals, however, the yolk sac seems to have a greater role in α-fetoprotein synthesis than does the shark yolk sac, and both avian and mammalian gastrointestinal tract seem to have a much smaller role than that in the shark. Thus, there appears to have been an orderly change in emphasis among the entodermally derived sites of α-fetoprotein synthesis during evolution, with a shift toward the yolk sac and away from the stomach.

Synthesis of IgM, IgG, IgE and IgD begins at approximately 10 to 11 weeks of gestation. At this stage of development, production of IgM occurs in the mesenteric lymph nodes, synthesis of IgG occurs in the mesenteric lymph nodes and the liver, and synthesis of IgE takes place in the liver and lung. By 17 to 18 weeks of gestation, lymphoid cells are distinguishable in the spleen, and the spleen then becomes the major single organ for IgM and IgG production. The serum level of IgG before 22 weeks of gestation is less than 200 mg%, but at 22 weeks there is a sudden activation of IgG transplacental transport mechanisms, and IgG rises rapidly to reach maternal levels by 26 weeks of gestation where it is maintained until birth (Fig. 2). It has been postulated by other investigators that each of the major im-

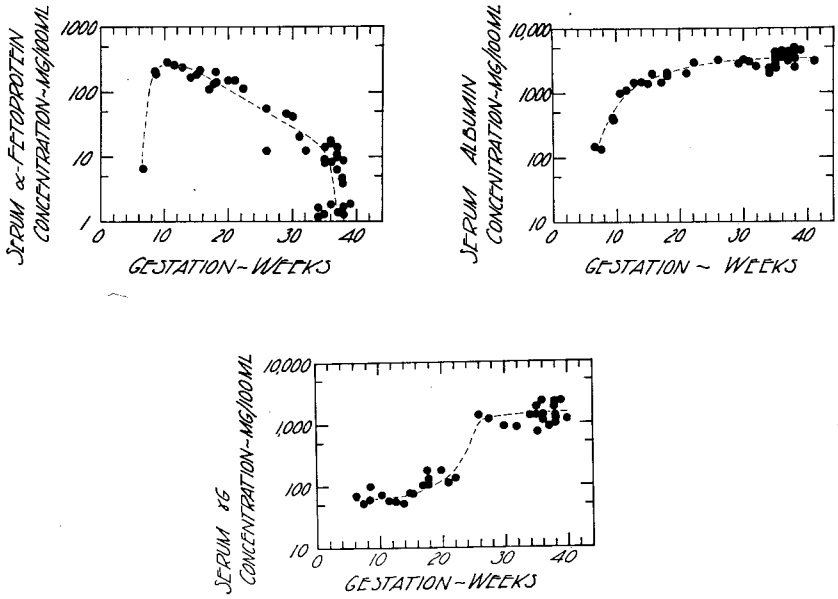

Fig. 2. Concentrations of α-fetoprotein, albumin and IgG in serum of the human conceptus as a function of gestation[1].

munoglobulin classes of man are synthesized by a single cell line which develops immunoglobulin synthesis sequentially. The finding that synthesis of IgM, IgG, IgE and IgD all begin at approximately the same time, however, seems to indicate instead that each immunoglobulin class is synthesized by a separate lymphoid cell line ; this concept is supported by the independent mode of inheritance of each immunoglobulin as indicated by studies of the immunodeficiency diseases of man[6], and by the observation that different classes of immunoglobulins appear in sharks which evolved more than 180 million years ago[7].

The serum α-fetoprotein level in the human conceptus at 6 to 7 weeks of gestation is approximately 7 mg%. It then rises rapidly to reach a maximum level of about 300 mg% at 10 to 13 weeks of gestation, which, unlike the later rapid rise in IgG level, is due entirely to endogenous synthesis. The serum α-fetoprotein concentration then falls exponentially with a half-life of approximately 32 days (Fig. 2). Since the overall synthesis of α-fetoprotein rises rapidly after 10 weeks of gestation to reach a sustained plateau between 22 and 32 weeks of gestation, the exponential decline in serum α-fetoprotein after 13 weeks of gestation is due to the fact that the rate of fetal growth exceeds the rate of increase in the total amount of α-fetoprotein synthesized. After 32 weeks of gestation, the level

of α-fetoprotein falls rapidly, indicating a sharp reduction in total α-fetoprotein production. Synthesis of α-fetoprotein is still evident at term in at least some normal fetuses, and further curtailment occurs at or near birth. However, nanogram levels of serum α-fetoprotein are still found in apparently normal adults.

When the fetus is delivered after spontaneous abortion or spontaneous premature labor, the fetal serum α-fetoprotein level in some cases may be considerably less than that in the fetus not subjected to such untoward events[8]. Whether the lower α-fetoprotein level is due to premature curtailment of α-fetoprotein synthesis in anticipation of or related to labor, or whether it is due to an increased permeability of the placenta to macromolecules with increased maternofetal transfer of α-fetoprotein, perhaps again related to the anomalous event, is not known. Other investigators have found that maternal serum α-fetoprotein levels are elevated above the normal for a given gestational state in more than half of those mothers carrying fetuses in distress[9]. Again, whether this reflects an increased permeability of the placenta with passage of α-fetoprotein from fetus to mother or may be due to maternal metabolic changes alone is not known.

It is important to note that the development of α-fetoprotein synthesis in the fetal rat, an animal also much studied in terms of this protein, is quantitatively different from that in the human conceptus. In the fetal rat, α-fetoprotein levels during the last half of gestation decline only slightly from the maximum level attained, then they fall sharply after delivery to approximately half the predelivery levels (Fig. 3), are then sustained until 8 to 14 days of age, after which they fall sharply once again[10]. This pattern can be readily understood when it is recognized that the yolk sac in the rat is a functional organ up to the time of delivery, and that both

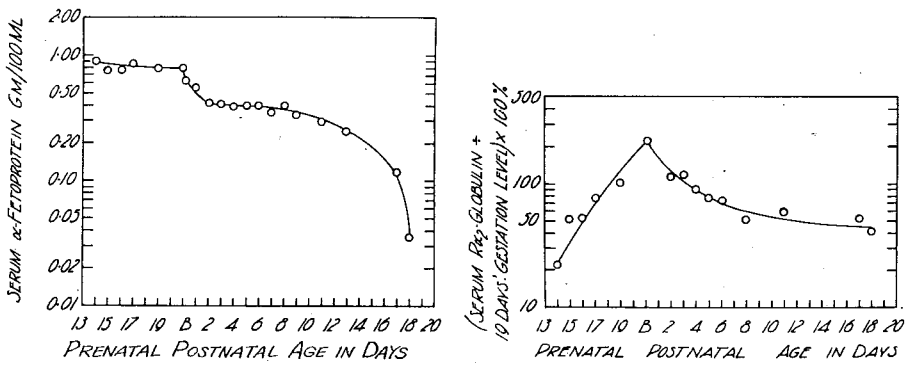

Fig. 3. Serum concentrations of α-fetoprotein and Rα_2-globulin (α_2H) in the rat as a function of age[10].

the yolk sac and the liver are primary sites for α-fetoprotein synthesis. During delivery, of course, the yolk sac, which forms one of the fetal membranes in the rat, is discarded, and hepatic synthesis in the newborn rat is curtailed at 8 to 14 days of age. In contrast, the fetal rat protein commonly termed α_2H rises continuously during gestation to reach a maximum level just prior to delivery, and although it, too, declines rapidly after birth, it does so continuously[9]. The protein α_2H is present in adult rats in much higher relative concentrations than is α-fetoprotein.

Cortisone acetate administered to pregnant rats just prior to parturition results in fetal suppression of α-fetoprotein synthesis. Similarly, cortisone acetate administered to newborn rats from 2 to 7 days of age results in marked depression of serum α-fetoprotein concentrations by the second day after injection. The newborn animals given cortisone are more hirsute, have atrophic thymuses and have smaller adrenals than normal at 4 to 6 days after the injection of cortisone, but low doses of cortisone acetate sufficient to involute the thymus do not have a significant effect on serum α-fetoprotein levels. Hydrocortisone succinate, estradiol, progesterone, testosterone, glucagon, epinephrine, bovine growth hormone, human chorionic prolactin and human chorionic gonadotropin have no obvious effect on α-fetoprotein synthesis. Sham operations under cold anesthesia in the newborn rat suppresses α-fetoprotein synthesis, although cold anesthesia alone does not, and adrenalectomy prevents this α-fetoprotein suppression. Since starvation alone also significantly inhibits α-fetoprotein production, it is possible that some of the fall in α-fetoprotein level following cortisone acetate may be due to the anorexigenic effect of this steroid. It is clear, in view of the delayed effect of cortisone acetate on α-fetoprotein production that cortisone acts only indirectly on the synthesizing pathway.

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